To: Examiner Gary B. Nickol, Ph. D., Group Art Unit 1642

Re: U.S. Patent Application No. 09/323,597

Discussion topics regarding Final Office Action mailed May 20, 2003 (Paper No. 37). Telephone interview September 9, 2003, at 1:00 pm Eastern time.

1) Regarding the enablement rejection (Paper No. 37, page 2 and following): In what way is the invention is not enabled? What additional information would one of skill in the art need to make and use the invention?

2) Why does expression of TMPRSS2 on normal tissue raise an enablement issue? (Paper No. 37, page 2, last paragraph and page 3, sentence bridging to page 4)

- Expression of the antigen on normal prostate tissue as well as malignant prostate tissue is not a problem. See Declaration of M. Faris Ph.D.

- The specification indicates that kidney/pancreas/lung expression of TMPRSS2 is 10- to 20-fold less than prostate expression (spec., page 5, lines 29-30).

- The issue is not that the antibody will destroy the entire prostate; even if it did, that would not be particularly detrimental to the individual. Surgical removal of the prostate also removes healthy tissue along with malignant tissue.

3) What is the relevance of antigenic heterogenicity (Paper No. 37, page 3, first complete paragraph) to the enablement rejection?

- The antibody binds to the antigen, and the antigen is strongly expressed on malignant tissue.

4) What remains to be done to achieve allowed claims?

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PATENT
Docket No. 51158200

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:	Examiner:
Serial No.:	Group Art Unit:
Filing Date:	
For:	

DECLARATION OF MARY FARIS, PH.D. CONCERNING NORMAL TISSUE EXPRESSION

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Mary Faris, declare as follows:

1. I hold the position of Group Leader-Target Validation at Agensys, Inc. This position requires me to generate *in vitro* models for the study of cancer, and to investigate the effect of specific genes and gene products on tumor development, growth, and progression. This position also requires me to attend national and international conferences addressing issues in cancer research conferences where established as well as cutting edge ideas are presented. I have a Ph.D. in Immunology and Microbiology from Ohio State University. In addition, I have held two postdoctoral fellowships, one at the University of Virginia and one at the University of California at Los Angeles, School of Medicine. I have worked in the field of molecular biology academically and professionally for over 15 years. A copy of my *curriculum vitae* is attached as Exhibit A.

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2. This submission is made in support of the proposition that targeted antitumor therapies are useful even when the targeted protein is expressed on normal tissues, what is more even if the normal tissue is from a vital organ. A vital organ is one that is necessary to sustain life, such as the heart or brain. A non-vital organ is one that can be removed whereupon the individual is able to survive without artificial life support. Examples of non-vital organs are ovary, breast, and prostate. The expression and targeting of two exemplary proteins will be discussed, HER2/neu and epidermal growth factor receptor (EGFR).

3. Herceptin® is an FDA approved pharmaceutical that has as its active ingredient an antibody which is immunoreactive with the protein known synonymously as HER2, HER2/neu, or erb-b-2. It is marketed by Genentech and has been a commercially successful antitumor agent. Herceptin sales reached almost $400 million in 2002 (see Exhibit B). The success of Herceptin is indicated by both the volume and trend of its sales figures. During the period it has been marketed, its sales numbers have consistently increased.

4. Herceptin is FDA approved as a treatment for HER2 positive metastatic breast cancer (see Exhibit C). However, the expression of HER2 is not limited to such tumors. The same protein is expressed in a number of normal tissues.

5. The diverse expression of the HER2/neu protein is indicated in Exhibit D.[1] Exhibit D provides data panels for three different GenBank deposits of HER2/neu sequence. The comparative data in Exhibit D show levels of HER2 above the median in numerous normal tissues. In particular, attention is called to the levels present in kidney and heart. The levels in kidney are consistently shown as higher than those in heart. It is emphasized that these values are for normal tissue; thus these tissues are present in *all human recipients* of Herceptin.

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6. The expression of HER2/neu in a diverse array of normal and malignant tissues was corroborated by studies conducted at Agensys, assignee of the present case, by use of RT-PCR (Exhibit F). Again, significant expression of HER2/neu was noted in heart and kidney. Further corroboration of normal expression of HER2/neu by immunohistochemistry is set forth in Exhibit G. In Exhibit G, positive staining for the presence of HER2/neu was found in normal kidney and colon tissue. Additional confirmation of the presence of HER2/neu in normal kidney is provided by Latif, et al.[2] As shown in this article (which evaluated whether renal cell carcinoma should be a preferred indication for anti-HER2 antibodies such as Herceptin), both protein and mRNA are produced in benign renal tissues. Notably, HER2/neu protein was strongly overexpressed in benign renal tissue (see page 8, left hand column last paragraph of Latif, et al.).

7. Despite the fact that HER2/neu is expressed in vital organs such as heart and kidney, Herceptin is very useful, FDA-approved, and commercially successful. The effect of Herceptin on cardiac tissue, i.e., "cardiotoxicity," has been a limited side effect to treatment. When patients were treated with Herceptin alone, a very low percentage of patients had any significant cardiotoxicity.

8. Of particular note, although the data shows that kidney tissue exhibits even higher expression than cardiac tissue, nephrotoxicity has not been an appreciable side effect of Herceptin treatment at all. In fact, of the diverse normal tissues in which HER2 is expressed, there is very little occurrence of any side effect. Only cardiac tissue has any appreciable side

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[1] The expression data in Exhibit D was established using gene chip technology; see Su, et al, PNAS *Proc. Natl. Acad. Sci. USA*, Vol. 99, Issue 7, 4465-4470, April 2, 2002, Exhibit E. The results for HER2 are available on the GNF Gene Expression Atlas website http://expression.gnf.org/cgi-bin/index.cgi.

[2] Latif, Z., et al., B.J.U. International (2002) 89:5-9 (Exhibit H)

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effect at all. A tissue such as kidney, where HER2/neu expression is appreciable, has not been the locus for any side effect.[3]

9. Taken together, this documentation establishes that production of a target protein such as HER2/neu on normal tissue, even vital normal tissue, does not defeat the utility of the protein as a therapeutic for certain tumors in which the protein is also expressed.[4] Such physiologic outcomes, where there is normal tissue expression of a cancer-associated protein target, are not unique to HER2/neu as will be discussed below.

10. Several anti-cancer therapeutic products that target the epidermal growth factor receptor (EGFR) are presently in clinical evaluation.[5] The small molecule product Iressa® received FDA approval[6] in May 2003. The rationale for EGFR-targeted anti-cancer treatments is both well known and well accepted.[7]

11. One EGFR-targeted anti-cancer treatment composition is Erbitux™ (also known as cetuximab or C225). The active ingredient in Erbitux is an antibody which is immunoreactive with the EGFR. Erbitux antibody has been shown to block the proliferation of various cancer cells.[8] The successful use of Erbitux is shown, for example, by a March 2003 $60 million commercialization payment (Exhibit K), as well as very exciting European clinical trial data disclosed in early 2003.[9] This data indicated that Erbitux was able to *affect shrinkage of tumor size by 50%*. Tumor size was decreased by 50% in 11% of patients who received Erbitux as a

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[3] See Exhibit G, the product information for Herceptin® for an overview of side effect issues

[4] This is particularly true where the target protein, as with HER2/neu is expressed at higher levels in tumor cells relative to normal tissue. In one embodiment, overexpression in tumor tissue can provide for altered, e.g., enhanced, protein availability for antibody binding.

[5] Baselega, J., Oncologist 7 (supp. 4):2-8 (2002) (Exhibit I)

[6] Iressa attaches itself to the EGF receptor inside the cell, which blocks the activation of tyrosine kinase, and switches off the signals from the EGFR.

[7] Id.

[8] Busam, et al. Br. J. Derm. 144:1169-1176 at 1169 (2001) (Exhibit J)

[9] C. Arnst "The War on Cancer: Good News, Glum Faces" BusinessWeek Online, June 3, 2003 <http://www.businessweek.com/technology/content/jun2003/tc2003063_1032.htm> (Exhibit K)

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single agent and in 23% of patients who received Erbitux in combination with chemotherapy.[10] In addition, tumor progression was delayed and life span appeared to be increased in the treated cancer patients. These are significant findings for a patient population with dire prognosis, few if any treatment options, and very short life expectancy.

12. EGFR is therefore being used and evaluated as a target for treatment of patients with breast, head and neck, lung, kidney and prostate cancer.[11] However, the expression of EGFR is not limited to such tumors. This protein is expressed in a diverse array of normal tissues.

13. EGFR protein is extensively expressed in adult humans. It is present on all epithelial and stromal cells, select glial and smooth muscle cells, oral and laryngeal mucosa[13]; brain;[14] liver,[15] prostate;[16] placenta;[17] stomach and colon;[18] and, skin.[19] It is to be noted that since it is expressed in these normal tissues, EGFR is present in all human recipients of any EGFR-targeted therapy.

14. Despite the fact that EGFR is expressed in numerous normal tissues, including vital tissues such brain and colon, therapeutics that target EGFR are very useful and are in active development. The only significant side effect of such therapeutics has been on skin as an acneiform rash.[20] This has merely been a side effect to treatment. This side effect is so minor

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[10] "Study backs ImClone drug's effectiveness" American Society of Clinical Oncology (ASCO) web page, June 2, 2003 < http://www.asco.org/ac/1,1003,_12-002122-00_18-0028202-00_19-0028203-00_20-001,00.asp> (Exhibit L)
[11] Busam, et al, *supra*
[12] Wells, A., Int. Biochem & Cell Biol. 31:637-643 at 640 (1999) (Exhibit M)
[13] Christensen, M., Dan Med Bull. 45(2):121-134 (Apr. 1998) (Exhibit N)
[14] Ferrer, et al., Prog. Neurobiol. 49(2):99-123 (Jun 1996) (Exhibit O)
[15] Luwar, et al., Cancer Res. 61:5355-5361 (July 15, 2001) (Exhibit P)
[16] De Miguel, et al., Cytokine 11(9):722-727 (Sep 1999) (Exhibit Q)
[17] Mauro, et al., Repro. Fertil. Devel. 7(6): 1465-1470 (1995) (Exhibit R)
[18] Challier and Menard, Frontiers in Biosci. 4:87-101 at sections 4.2 and 4.3 (January 15, 1999) (Exhibit S)
[19] Jost, et al. Eur. J. Dermatol. 10(7):505-510 (Oct-N v 2000); Luwar, et al., Cancer Res. 61:5355-5361 (July 15, 2001) (Exhibit T)
[20] Busam, et al, *supra;* Van Doorn, et al., Br. J. Derm. 147:598-601 (2002) (Exhibit U)

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that it is used as an indication that therapeutically effective dosage levels have been achieved.[21] Notably, the side effect is actually capitalized on as a relatively innocuous signal that an individual has achieved a therapeutically effective dose.

15. The data on EGFR establishes that production of a target protein such as EGFR on normal tissue, even vital normal tissues, does not preclude the utility of the protein as a therapeutic for certain tumors in which the protein is also highly expressed.[22]

16. Thus, targeted antitumor therapies are useful even when the targeted protein is expressed on normal tissues, even normal vital organ tissues. The ability to use a cancer-associated protein in this manner is not unique to any particular protein. The existence of expression of a protein on a normal tissue, even a vital organ tissue, still allows for meaningful and successful use of that protein as a therapeutic target.

17. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are

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[21] Abgenix Press release 20 Aug 2002 <http://ir.abgenix.com/phoenix.zhtml?c=91622&p=IROL-NewsText&t=Regular&id=381536&> (Exhibit V)
[22] See footnote 4, *supra*

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punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at Santa Monica, California, this __th day of _____ 2003.

_____
Mary Faris, Ph.D.

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Re: U.S. Patent Application No. 09/323,597

The following topics were discussed in the telephone interview of September 9, 2003. Discussion between Examiner Nickol, Agensys attorney Timothy Lithgow, and agent for applicants Robert Cerpa.

(Rejections from Final Office Action mailed May 20, 2003, Paper No. 37)

1) Regarding the enablement rejection (Paper No. 37, page 2 and following): In what way is the invention is not enabled? What additional information would one of skill in the art need to make and use the invention?

Results of Sept. 9 interview:
Issue not resolved. In the discussion, the claim was reviewed element-by-element. It is our understanding that Examiner Nickol agrees that one can raise antibodies to the antigen. It is also our understanding that Examiner Nickol agrees that one can formulate the antibodies in a vehicle and administer the antibodies. However, Examiner Nickol maintains that the claim is not enabled. Draft Declaration of Dr. Art Raitano (attached) addresses this point, and indicates that the claim as written is enabled to one of skill in the art.

We respectfully request clarification of what is not enabled. Since the rejection is framed as an enablement rejection, and not a utility rejection, presumably the Examiner agrees that the invention actually works for the claimed purpose. If the enablement rejection is issued under a Wands analysis, which Wands factor(s) is at issue?

Examiner Nickol also indicated that there was a policy in the Group Art Unit per Ex. Stanton, that animal model data would be required to demonstrate enablement of the claim. Robert Cerpa contacted Examiner Brian Stanton to inquire about this policy. Ex. Stanton indicated that each case is evaluated on its own merits, and to contact Ex. Anthony Caputa regarding the case. Examiner Caputa stated that an analysis under *In re Wands* is generally applied, and indicated that this could be discussed in an interview with himself, Examiner Nickol, and the attorney and agent for Agensys.

2) Why does expression of TMPRSS2 on normal tissue raise an enablement issue? (Paper No. 37, page 2, last paragraph and page 3, sentence bridging to page 4)

- Expression of the antigen on normal prostate tissue as well as malignant prostate tissue is not a problem. See Declaration of M. Faris Ph.D.
- The specification indicates that kidney/pancreas/lung expression of TMPRSS2 is 10- to 20-fold less than prostate expression (spec., page 5, lines 29-30).
- The issue is not that the antibody will destroy the entire prostate; even if it did, that would not be particularly detrimental to the individual. Surgical removal of the prostate also removes healthy tissue along with malignant tissue.

Results of Sept. 9 interview:
Status of this issues is unclear. Ex. Nickol indicated that normal tissue expression was not a basis for the enablement rejection, and that the Declaration by Dr. Mary Faris was not relevant to the rejection at hand. Normal expression had been cited as an issue in the past. If this earlier basis for rejection is overcome, Applicants gratefully acknowledge this fact.

3) What is the relevance of antigenic heterogeneity (Paper No. 37, page 3, first complete paragraph) to the enablement rejection?

- The antibody binds to the antigen, and the antigen is strongly expressed on malignant tissue.

Results of Sept. 9 interview:
While this topic was not discussed at length, it is unclear how antigenic heterogeneity affects enablement of the invention. The Examiner agreed that antibodies could be raised to the antigen; the degree of antigenic heterogeneity will determine whether the invention will work (i.e. utility), not whether one of skill in the art can make and use the invention. Again, as normal expression had been cited as an issue in the past. If this earlier basis for rejection is overcome, Applicants gratefully acknowledge this fact.

4) What remains to be done to achieve allowed claims?

Results of Sept. 9 interview:
Examiner Nickol stated that, before a claim that can read on therapy could be allowed, animal model data or human data would need to be presented. He also stated that data commensurate with the full scope of the claim would be required; i.e., if *in vitro* use were claimed, then in vitro data would need to be presented. Is this indeed the standard that will be applied? Why is the independent claim being prosecuted as if it had limitations that are not in it? What about the other non-therapy aspects of the claim as written? This issue is dealt with in the Draft Declaration of Dr. Art Raitano.

Pending and proposed claims for USSN 09/323,597,
Morrison & Foerster reference no. 51158-20008.00

Pending claims 72-82:

72. A method for inhibiting the growth, viability and/or survivability of cancer cells that express the nucleotide sequence SEQ. ID. No.: 1 or the cDNA in ATCC deposit 207097 (20P1F12/TMPRSS2), the method comprising:

administering to the cancer cells an antibody or fragment thereof that specifically binds to a 20P1F12/TMPRSS2 protein, thereby inhibiting the growth, viability and/or survivability of said cancer cells.

73. The method of claim 72, wherein said antibody or fragment is a monoclonal antibody, or fragment thereof.

74. The method of claim 72, wherein said antibody or fragment is a recombinant protein comprising the antigen-binding region of an antibody that specifically binds to 20P1F12/TMPRSS2 protein.

75. The method of claim 72, wherein said antibody or fragment is labeled with a detectable marker.

76. The method of claim 72, wherein said antibody or fragment is conjugated with a cytotoxic agent.

77. The method of claim 72, wherein said antibody or fragment is a human antibody or fragment.

78. The method of claim 72, wherein said antibody or fragment is administered by administering a recombinant polynucleotide that encodes the antibody or fragment thereof.

79. The method of claim 72 wherein the cancer cells are in a mammal.

80. The method of claim 79, wherein the mammal is a human and the said antibody or fragment is a recombinant protein which comprises a chimeric or humanized antibody.

81. The method of claim 80, wherein said antibody or fragment is administered with a pharmaceutically acceptable carrier.

82. The method of claim 80, said antibody or fragment is administered as the composition in a human patient dose.

Proposed new claims 85-87:

85. A method for characterizing an antibody that specifically binds a polypeptide encoded by the nucleotide sequence SEQ. ID. No.: 1 or the cDNA in ATCC deposit 207097 (20P1F12/TMPRSS2), the method comprising:

providing cancer cells that express a polypeptide encoded by the nucleotide sequence SEQ. ID. No.: 1 or the cDNA in ATCC deposit 207097 (20P1F12/TMPRSS2);

providing an antibody that specifically binds a polypeptide encoded by the nucleotide sequence SEQ. ID. No.: 1 or the cDNA in ATCC deposit 207097 (20P1F12/TMPRSS2);

administering to the cancer cells an antibody or fragment thereof that specifically binds to a 20P1F12/TMPRSS2 protein; and,

identifying that the antibody inhibits growth, viability and/or survivability of said cancer cells.

86. A method for inhibiting the growth, viability and/or survivability of cancer cells that express the nucleotide sequence SEQ. ID. No.: 1 or the cDNA in ATCC deposit 207097 (20P1F12/TMPRSS2), the method comprising:

administering to the cancer cells *in vitro* an antibody or fragment thereof that specifically binds to a 20P1F12/TMPRSS2 protein, thereby inhibiting the growth, viability and/or survivability of said cancer cells.

87. The method of claim 86, further comprising the step of:

evaluating the mechanism by which the antibody or fragment thereof that specifically binds to a 20P1F12/TMPRSS2 protein inhibits the growth, survivability, and/or viability of cancer cells that express the nucleotide sequence SEQ. ID. No.: 1 or the cDNA in ATCC deposit 207097 (20P1F12/TMPRSS2).